REMARKS

Claims 288-298 are pending in the application. Claims 1-287 have been canceled without prejudice. New claims 288-298 have been added. The right to prosecute the subject matter of any canceled claim in one or more continuation, continuation-in-part or divisional applications is hereby reserved. No new matter has been added.

Support in the specification for the new claims can be found, for example, as indicated in the table, below.

Claim	Support
288	Page 6, lines 8-20; Page 10, line 4; Page 11, lines 1, 3, and 31; Page 12, lines 4-11, 17-18, and 26; Page 14, lines 23-24; Page 15, lines 26-28; Page 18, lines 5, 13-32; Page 19, lines 1-8 and 28-31; Page 20, lines 23-25; Page 21, lines 12 and 31; Page 24, lines 8-13; Page 25, lines 4-20; Page 40, line 18 to Page 41, line 12; Page 42, lines 23-27; Page 43, lines 1-12; Page 49, line 21; Page 50, lines 27 to Page 51, line 12; Examples 1-27, 46-76, 96-134, and 149-152
289	Page 30, line 9, et seq.
290	Page 18, lines 16-18; Page 30, line 10, et seq.
291	Page 18, line 24
292	Page 18, lines 24-25; Page 37, line 12; Page 40, line 21; Page 41, line 6; Page 43, line 6; Page 44, line 28; Page 47, line 25; Page 49, line 11, et seq.
293	Page 22, lines 8-9; Examples 135-145
294	Page 22, lines 9-11; Examples 111-118
295	Page 12, lines 4-11; Page 22, line 31 to Page 23, line 1; Examples 149-152
296	Page 20, line 25

297	Page 27, lines 10-11 and 30 to Page 28, line 27; Examples 105-106
298	Page 32, line 13, et seq.

Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 199, 201, 202, 206-213, and 225-287 have been rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. Claims 199, 201, 202, 206-213, and 225-287 have been canceled without prejudice, rendering the rejection of these claims moot.

Furthermore, none of new claims 288-298 recites the language, "bilayer vesicle," "the surface of the vesicle carries a net electric charge and wherein the macromolecule carries a net electric charge and the net electric charge of the surface of the vesicle and the net electric charge of the macromolecule have the same sign," "fatty acid", "Brij-type," or "Myrj-type."

In view of the above, it is believed that the rejection under 35 U.S.C. § 112, second paragraph, has been overcome and should be withdrawn.

Rejection Under 35 U.S.C. §102(b)

Claims 199, 201-202, 206-208, 213, 225, 227, 229-230, 232, 235, 237, 240, 242-245, 250, 252-253, 257-258, 261, 263-268, 271-273, 278, 280-282 and 287 have been rejected under 35 U.S.C. 102(b) as being allegedly anticipated by U.S. Patent No. 4,731,210 to Weder *et al.* ("Weder"). Claims 199, 201-202, 206-208, 213, 225, 227, 229-230, 232, 235, 237, 240, 242-245, 250, 252-253, 257-258, 261, 263-268, 271-273, 278, 280-282 and 287 have been canceled without prejudice, rendering the rejection of these claims moot.

Furthermore, none of new claims 288-298 is anticipated by Weder. Weder's methods require reducing the amount of surfactant to lipid in a composition (see column 3, lines 7-12, and column 4, lines 52-56.) To accomplish this, Weder specifically discloses four methods, A-D, at column 4, lines 57-68. Method A of Weder, disclosed at column 5 lines 5-64 and example 1, subjects the composition to dilution. Method B of Weder is disclosed at column 5, line 65 to column 6, line 33 and examples 3 and 4. Method B subjects the composition to a.) a sudden change in temperature, b.) an addition of absorbents such as activated carbon, c.) a sudden change in pH, or d.) an addition of a further substance which complexes the surfactant. Method C of Weder, disclosed at column 6, line 34 to column 7, line 45 and example 2, subjects the composition to counter-current dialysis. Weder specifically describes the dialysis method at column 6, lines 34-42, stating that dialysis requires a semipermeable membrane that *retains* a

bilayer-forming substance and a pharmaceutical substance. In stark contrast, the claimed method recites filtering a composition *through* a filtering material. Method D of Weder, disclosed at column 7, line 46 to column 8, line 30 and example 5, subjects the composition to merely an increase in the concentration of bilayer-forming substance. Accordingly, none of Weder's Methods A-D discloses the step of filtering a composition through a filtering material, as recited in the present claims. Furthermore, none of new claims 289-298 is anticipated by Weder, as new claims 289-298 depend from new claim 288.

Rejection Under 35 U.S.C. §103(a)

Claims 199, 201, 202, 206-213 and 225-287 have been rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Weder alone or in combination with WO 92/03122 to Cevc ("Cevc"), or vice versa. Claims 199, 201, 202, 206-213 and 225-287 have been canceled without prejudice, rendering the rejection of these claims moot.

Moreover, it is believed that none of new claims 288-298 is obvious over Weder alone or in combination with Cevc.

The consistent criterion for a determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in the light of the prior art. *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

Weder alone or in combination with Cevc does not render the present claims obvious. As stated above, Weder's methods require reducing the amount of surfactant to lipid in a composition. Method A of Weder subjects the composition to dilution. Method B of Weder subjects the composition to a.) a sudden change in temperature, b.) an addition of absorbents such as activated carbon, c.) a sudden change in pH, or d.) an addition of a further substance which complexes the surfactant. Method C of Weder subjects the composition to counter-current dialysis. Weder specifically discloses the dialysis method at column 6, lines 34-42, stating that dialysis requires a semipermeable membrane that *retains* a bilayer-forming substance and a pharmaceutical substance. In stark contrast, the claimed method recites filtering a composition *through* a filtering material. Moreover, Method C of Weder is inferior to the presently claimed methods because Weder's Method C cannot remove from the composition unwanted species

whose size is equal to or larger than that of the vesicles. Method D of Weder subjects the composition merely to an increase in the concentration of bilayer-forming substance. Accordingly, none of Methods A-D suggests, much less teaches, filtering a composition through a filtering material. Therefore, in light of the above, Weder does not in any way suggest carrying out the presently claimed methods, which recite filtering a composition through a filtering material, much less with a reasonable likelihood of success.

The presently claimed methods are not obvious over the methods of Cevc. Cevc discloses filtration *after* insulin is added to a lipid and a surfactant, for example in Examples 166 and 236. In stark contrast, the methods of the presently pending claims relate to filtering a composition comprising a phosphatidylcholine, a surfactant, and water through a filtering material, and then allowing the filtered composition and a macromolecule to contact each other and form macromolecule-bound vesicles. Unlike the method of Cevc, the composition of the present claims is filtered *before* it is contacted with the macromolecule.

Weder does not cure the deficiency of Cevc because Weder does not teach filtration through a filtering material. Cevc does not cure the deficiency of Weder because Cevc teaches filtration *after* insulin is added to a lipid and a surfactant. Therefore, in view of the above, Weder or Cevc, alone or in combination with either, does not make the presently pending claims obvious.

Provisional Obviousness-Type Double Patenting Rejections

Claims 199, 201, 202, 206-213 and 225-287 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 31, 38 and 70-76 of allegedly copending application no. 09/621,574 (the "'574 application").

Claims 199, 201, 202, 206-213 and 225-287 have been canceled without prejudice, rendering the provisional rejection moot.

The '574 application was abandoned; however, a petition to revive the '574 application was filed on July 5, 2006. The petition was accompanied by a reply in the form of a continuation application, U.S. Application No. 11/481,804 (the "'804 application"), along with a preliminary amendment, a copy of which is enclosed, that canceled claims 1-30 and added new claims 31-77. The present new claims 289-298 are patentably distinct from claims 31-77of the '804 application

because none of claims 31-77 of the '804 application suggests a method for making macromolecule-bound vesicles, where the method comprises filtering a composition comprising a phosphatidyl choline, a surfactant, benzyl alcohol, and water through a filtering material and allowing the resultant filtered composition and a macromolecule to contact each other. Furthermore, if the petition to revive the '574 application was granted, the presently pending claims are patentably distinct from the claims of the '574 application for the reasons discussed above.

Claims 199, 201, 202, 206-213 and 225-287 have also been provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-66, 80-81 and 88-100 of copending application no. 10/357,618 (the "'618 application").

Claims 199, 201, 202, 206-213 and 225-287 have been canceled without prejudice, rendering the provisional rejection moot.

Furthermore, it is believed that new claims 288-298 are patentably distinct from the claims of the '618 application. New claim 288 recites a method for making macromolecule-bound vesicles, where the method comprises filtering a composition comprising a phosphatidyl choline, a surfactant, *benzyl alcohol*, and water. In stark contrast, none of the claims of the '618 application suggests a composition comprising *benzyl alcohol,* much less a method comprising filtering such a composition and allowing the filtered composition and a macromolecule to contact each other and form macromolecule-bound vesicles.

In light of the forgoing remarks, it is believed that the provisional rejections under the judicially created doctrine of obviousness-type double patenting over the '574 application and the '618 application have been overcome and should be withdrawn.

Conclusion

It is respectfully requested that the Examiner enter the present amendment in light of the foregoing remarks and it is believed that all the claims are in condition for allowance. If the Examiner believes that a telephone interview would help expedite the prosecution of the claims, the undersigned attorney would be grateful for the opportunity to discuss any outstanding issues.

Please charge any fees due or credit any overpayments in connection with the above-identified application to Wilmer Cutler Pickering Hale and Dorr LLP Deposit Account No. 08-0219.

Respectfully submitted,
WILMER CUTLER PICKERING HALE AND DORR LLP

Reg. No. 36,343

Date: February 9, 2007

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	G. Cevc		
U.S.S.N.:	Not yet assigned	Group No.:	Not yet assigned
FILED:	Herewith	Examiner:	Not yet assigned

FOR: PREPARATION FOR THE APPLICATION OF AGENTS IN MINI-DROPLET

Particulars of Prior Application:
Serial No.: 09/621,574
Filed: July 21, 2000
Group No.: 1615
Examiner: G.S. Kishore

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

PRELIMINARY AMENDMENT

Please make the following changes before examining the above-identified patent application.

Amendments to the Specification begin on page 2 of this paper.

Amendments to the Claims are reflected in the listing of claims which begins on page 3 of this paper.

Remarks/Arguments begin on page 7 of this paper.

Amendments to the Specification

Please amend the Specification as follows:

Please insert the following new section entitled "Cross-Reference to Related Case" on page 1, beneath the title.

Cross-Reference To Related Case

This is a continuation of and claims the benefit of and priority to U.S. Patent Application Serial No. 09/621,574, filed on July 21, 2000, which is a continuation of U.S. Patent Application Serial No. 07/844,644, filed on April 8, 1992, the entirety of which are incorporated herein by reference.

Amendments to the Claims

In the claims:

This listing of claims will replace all prior versions and listings of claims in the application:

1-30 (Canceled)

31. (New) A preparation suitable for transporting active agents through permeability barriers, comprising a plurality of transfersomes in a medium, said transfersomes comprising a pharmaceutically acceptable lipid and a pharmaceutically acceptable surfactant which is compatible with said lipid, the ratio of said lipid to said surfactant enabling said transfersomes to undergo sufficient deformation to enable said transfersomes to pass as an entity through a permeability barrier which has pores smaller than the size of said transfersomes, wherein the total concentration of said lipid in said medium is from about 0.1% to about 30%, by weight and the ratio of lipid to surfactant is from about 5:1 to about 1:500.

32. (New) The preparation as claimed in claim 31, wherein said transfersomes are unilamellar.

33. (New) The preparation as claimed in claim 31, wherein said permeability barrier is mammalian skin.

34. (New) The preparation as claimed in claim 31, wherein the concentration of said surfactant is between 20 and 50 mol-% of the concentration of said surfactant which would be required for causing said lipid to be solubilized, and the edge tension of said transfersomes is about 10 Piconewton or less.

35. (New) The preparation as claimed in claim 31, further comprising an active agent associated with said transfersomes, said active agent being contained in the interior of said transfersome in an outer membrane of said transfersome, or both.

36. (New) The preparation as claimed in claim 31 wherein the total concentration of said lipid in said medium is between 0.1 and 15 weight-%.

37. (New) The preparation as claimed in claim 31, wherein the total concentration of said lipid in said medium is between 5 and 10 weight-%.

38. (New) The preparation as claimed in claim 31, wherein the total concentration of said lipid in said medium for application on plants is between 0.000001 and 10 weight %.

39. (New) The preparation as claimed in claim 31, wherein the total concentration of said lipid in said medium for application on plants is between 0.001 and 1 weight %.

40. (New) The preparation as claimed in claim 31, wherein the total concentration of said lipid in said medium for application on plants is between 0.01 and 0.1 weight-%.

41. (New) The preparation as claimed in claim 35 wherein said active agent is a growth modulating substance for living organisms.

42. (New) The preparation as claimed in claim 31 wherein said active agent exerts biocidal activity as an insecticide, pesticide, herbicide or fungicide.

43. (New) The preparation as claimed in claim 31 wherein the active agent is an attractant

44. (New) The preparation as claimed in claim 31 wherein the active agent is a pheromone.

45. (New) A method of manufacturing preparations for the transport of agents through permeability barriers:

(A) forming transfersomes by combining a lipid and a surfactant that can solubilize said lipid in a suitable medium and determining the ratio of lipid to surfactant which enables transfersomes formed by combining said lipid and said surfactant in said medium to undergo sufficient deformation to enable said transfersomes to pass as an entity through a permeability barrier which has pores smaller than the size of said transfersomes, and

(B) preparing said transfersomes in said medium such that the total concentration of said lipid in said medium is from about 0.1% to about 30%, by weight.

46. (New) The method as claimed in claim 45 wherein said transfersomes are unilamellar .

47. (New) The method of claim 45 wherein the stability and the permeation capacity of said transfersomes are determined by means of mechanical fragmentation.

48. (New) The preparation as claimed in claim 31 wherein said preparation comprises at least one antidiabetic agent.

49. (New) The method as claimed in claim 45 wherein said transfersomes have a double layer structure.

50. (New) The method as claimed in claim 45 wherein said lipid is a synthetic lipid.

51. (New) The method as claimed in claim 45 wherein said lipid comprises a glyceride.

52. (New) The method as claimed in claim 45 wherein said lipid is selected from the group consisting of glycerophospholipid, isoprenoidlipid, sphingolipid, a sulfur-containing lipid, and a carbohydrate-containing lipid.

53. (New) The method as claimed in claim 45 wherein said lipid comprises a fatty acid.

54. (New) The method as claimed in claim 45 wherein said lipid is selected from the group consisting of phosphatidylcholine, phosphatidylethanolamine, phosphatidyglycerol, phosphatidylinositol, phosphatidic acid, phosphatidylserine, sphingomyeline, sphingophospholipid, glycosphingolipid, cerebroside, ceramidepolyhexoside, sulfatide, sphingoplasmalogene, a ganglioside, and a glycolipid.

55. (New) The method as claimed in claim 45 wherein said lipid is selected from the group consisting of dioleoyl lipid, dilinoleyl lipid, dilinolenyl lipid, dilinolenoyl lipid, diarachidoyl lipid, dimyristoyl lipid, dipalmitoyl lipid, distearoyl lipid, phospholipid, diacyl lipid and dialkyl lipid.

56. (New) The method as claimed in claim 45 wherein surfactant is selected from the group consisting of nonionic surfactants, zwitterionic surfactants, anionic surfactants and cationic surfactants.

57. (New) The method as claimed in claim 45 wherein said surfactant is selected from the group consisting of a long-chain fatty acid, a long-chain fatty alcohol, an alkyl-trimethyl-ammonium-salt, an alkylsulfate salt, a cholate-, a deoxycholate-, a glycodeoxycholate-, taurodeoxycholate, dodecyl-dimethyl-aminoxide, decanoyl-N-methylglucamide, dodecanoyl-N-methylglucamide, N-dodecyl-N, N-dimethylglycine, 3-(hexadecyldimethylammonio)-propane-sulfonate, N-hexadecyl-sulfobetaine, nonaethylene-glycoloctylphenylether, nonaethylene-dodecylether, octaethyleneglycolisotridecylether, octaethylenedodecylether, polyethlene glycol-20-sorbitanemonolaurate, polyhydroxyethylene-cetylstearyl ether polyhydroxyethylene-4-laurylether, polyhydroxyethylene-23-laurylether, polyhydroxyethylene-8-stearate, polyhydroxyethylene-40-stearate, polyhydroxyethylene-100-stearate, polyethoxylated castor oil 40, polyethoxylated hydrated castor oil, sorbitanemonolaurate, lauryl-salts, oleoylsulfate-salts, sodium deoxycholate, sodium glycodeoxycholate, sodium oleate, sodium elaidate, sodium linoleate, sodium laurage, nonaethylene-dodecylether, polyethylene glycol-20-sorbitane-

monooleate, polyhydroxyethylene-23-laurylether, polyhydroxyethylene-40-stearate, a sorbitane phospholipid, a monolaurate phospholipid, and a lysophospholipid.

58. (New) The method as claimed in claim 45 wherein said agent comprises between 1 and 500 I.U. insulin/ml.

59. (New) The method as claimed in claim 45 wherein said agent comprises between 20 and 100 I.U. insulin/ml .

60. (New) The method as claimed in claim 45 wherein the total concentration of said lipid in the preparation is between 0.1 and 20 weight-%.

61. (New) The method as claimed in claim 45 wherein the total concentration of said lipid in the preparation is between 0.5 and 15 weight-%.

62. (New) The method as claimed in claim 45 wherein the concentration of said lipid in the preparation is between 2.5 and 10 weight %.

63. (New) The method as claimed in claim 45 wherein said lipid is selected from the group consisting of phosphatidylcholine and phosphatidylglycol.

64. (New) The method as claimed in claim 45 wherein said surfactant is selected from the group consisting of lysophosphatidic acid, lysophosphoglycerol, deoxycholate, glycodeoxycholate, laurate, myristate, oleate, palmitoleate, phosphate salts thereof, sulfate salts thereof, a Tween-surfactant and a Myrj-surfactant.

65. (New) The method as claimed in claim 45 wherein the radius of said transfersomes in the preparation is between approximately 50 and approximately 200 nm.

66. (New) The method as claimed in claim 45 wherein the radius of said transfersomes in the preparation is between approximately 100 and approximately 180 nm.

67. (New) The preparation as claimed in claim 31 wherein the ratio of lipid to surfactant is from about 5:1 to about 1:5.

68. (New) The preparation as claimed in claim 31 wherein the ratio of lipid to surfactant is from about 12:1 to about 1:8.

69. (New) The preparation as claimed in claim 31 wherein said agent comprises between 1 and 500 I.U. insulin/ml.

70. (New) The preparation as claimed in claim 31 wherein the radius of said transfersomes in the preparation is between approximately 50 nm and approximately 340 nm.

71. (New) The preparation as claimed in claim 31 wherein the active agent is selected from the group consisting of an adrenocorticosteroid or its analogues, an androgen, an antiandrogen, an anabolic steroid, an anaesthetic, and analgesic, an antiallergic, an antiarrhythmic, an antiarterosclerotic, an antiasthmatic, an antidepressant, an antipsychotic, and antidiabetic, an antidote, and antiemetic, and antifibrinolytic, an anticonvulsant, and anticholinergic, an enzyme, a coenzyme, an enzyme inhibitor, an antihistaminic, and antihypertonic, and anticoagulant, an antimycotic, and anti-Parkinson agent, an antiphlogistic, an antipyretic, an antirheumatic, and antiseptic, a respiratory agent, a chemotherapeutic, a coronary dilator, an antineoplastic, a diuretic, a ganglium blocker, a glucocorticoid, and immunologically active substance, a contraceptive, a morphine-antagonist, a muscle relaxant, a narcotic, a nucleotide, a neurotransmitter, an ophthalmic, a sympaticomimetic, a sympathicocylytic, a parasympaticomimetic, a parasympathicolytic, a protein, a protein derivative, an anti-psoriatic, a psychostimulant, a sleep-inducing agent, a sedating agent, a spasmolytic, a tuberculosis preparation, a vasoconstrictor, a vasodilator, a wound-healing substance and combinations thereof.

72. (New) A preparation suitable for transporting active agents through permeability barriers, comprising a plurality of transfersomes in a medium, said transfersomes comprising a pharmaceutically acceptable lipid and a pharmaceutically acceptable surfactant which is compatible with said lipid, the ratio of said lipid to said surfactant enabling said transfersomes to undergo sufficient deformation to enable said transfersomes to pass as an entity through a permeability barrier which has pores smaller than the size of said transfersomes, wherein the total concentration of said lipid in said medium is from about 0.1% to about 30% by weight, the ratio of said lipid to said surfactant being greater than the ratio of lipid to surfactant attained at a first maximum permeability resistance and less than the ratio of lipid to surfactant attained at a second maximum permeability resistance.

73. (New) A preparation suitable for transporting active agents through permeability barriers, comprising a plurality of transfersomes in a medium, said transfersomes comprising a pharmaceutically acceptable lipid and a pharmaceutically acceptable surfactant which is compatible with said lipid, the ratio of said lipid to said surfactant enabling said transfersomes to undergo sufficient deformation to enable said transfersomes to pass as an entity through a

permeability barrier which has pores smaller than the size of said transfersomes, wherein the total concentration of said lipid in said medium is from about 0.1% to about 30% by weight and the ratio of lipid to surfactant is from about 5.5:1 to about 1:500.

74. (New) The method as claimed in claim 45 wherein the radius of said transfersomes in the preparation is between approximately 50 and approximately 340 nm.

75. (New) The method as claimed in claim 45 wherein the ratio of lipid to surfactant is from about 5:1 to about 1:5.

76. (New) The method as claimed in claim 45 wherein the ratio of lipid to surfactant is from

77. (New) The method as claimed in claim 45 further comprising varying the ratio of lipid to surfactant in said transfersomes to obtain a first maximum permeability resistance, increasing the amount of surfactant relative to said lipid until a second maximum permeability resistance is obtained, and manufacturing transfersomes having a ratio of lipid to surfactant of said transfersomes which is greater than the ratio of lipid to surfactant attained at the first maximum permeability resistance and less than the ratio of lipid to surfactant attained at the second maximum permeability resistance.

REMARKS

Applicants file this continuation based on co-pending U.S.S.N. 09/621,574 filed on July 21, 2000.

Applicants amend the Specification to insert the proper claim for priority.

Applicants have calculated the filing fees for this continuation based on the number of claims after the entry of this Preliminary Amendment. Applicants believe that no additional fees are due.

It is believed the application is in condition for immediate allowance, which action is earnestly solicited.

Dated: July 5, 2006

Respectfully submitted,
By _____

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